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Characteristics and outcomes of COVID-19 patients with IPF: a multi-center retrospective study

Aykut Cilli[1], Ismail Hanta[2], Fatih Uzer[1], Funda Coskun[3], Can Sevinc[4], Pelin Pınar Deniz[2], Mehmet Parlak[1], Ersoy Altunok[2], Kemal Can Tertemiz[4], Ahmet Ursavas[3]

1. Department of Respiratory Disease, Akdeniz University, Antalya, Turkey
2. Department of Respiratory Disease, Cukurova University, Adana, Turkey
3. Department of Respiratory Disease, Uludag University, Bursa, Turkey
4. Department of Respiratory Disease, Dokuz Eylul University, Izmır, Turkey

Corresponding author: Aykut Cilli

Email: acilli@akdeniz.edu.tr

Telephone:00902422496690

Adress: Akdeniz University, Department or Respiratory Disease, Antalya, Turkey

ABSTRACT

Background: There are few data on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (COVID-19) infection in patients with idiopathic pulmonary fibrosis (IPF). The objective of this study is to describe the characteristics and outcomes of IPF patients confirmed COVID-19 infection.

Methods: In this retrospective, multi-center, cohort study, patients from 4 hospital medical records with known IPF and a COVID-19 diagnosis were identified. Demographic and clinical outcome data were abstracted through a review of electronic medical records.

Results: Records for 46 patients with IPF and COVID-19 were abstracted. The mean age was 65±10 years. The most common symptom was dyspnea, followed by fever and cough. Ground-glass opacities (n=35, 83.3%) and consolidations (n=11, 26.1%) were the main imaging features of the disease in thorax computed tomography (CT). Twenty-four patients (52.1%) required hospitalization. Among the hospitalized patients, 16 (66.6%) were admitted to the intensive care unit (ICU), and 10 (41.6%) underwent invasive mechanical ventilation. Thirteen patients (28.2%) died of COVID-19 complications. Mortality rate was significantly associated with lower DLCO/VA, long term oxygen therapy and consolidation finding on CT of thorax ($p<0.05$). On multivariable analysis, neither factor was associated with hospitalization or mortality.

Conclusions: IPF patients represent a vulnerable population for COVID-19, according to the high rate of hospitalization, ICU requirement and mortality rate. Measures to minimize the risk of COVID-19 infection remain key to protect IPF patients.

Key words: interstitial lung disease, idiopathic pulmonary fibrosis, outbreak, pandemic, SARS-CoV-2

1. INTRODUCTION

Globally, there have been 240 million confirmed cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (COVID-19) including nearly 5 million deaths [1]. Various studies and meta-analyses have demonstrated that elderly people and those with pre-existing chronic respiratory diseases are considered as risk factors for the disease severity, poor prognosis, and mortality in COVID-19. It has been shown that prognosis of COVID-19 patients with pre-existing interstitial lung disease (ILD) is significantly worse than that of non-ILD patients [2–4]. Preexisting lung damage, impaired pulmonary functions or acute exacerbation induced by viral infection in ILD may cause more severe disease [2,3]. In a multinational study, Drake and colleagues assessed in-hospital mortality of 161 patients with ILD hospitalized with COVID-19 [4]. Sixty-eight (42.2%) of 161 patients had idiopathic pulmonary fibrosis (IPF). They found that patients with ILD have significantly higher in-hospital mortality compared with those without ILD (49% vs 35%). Similarly, a study from United States examined mortality among 46 ILD patients diagnosed with COVID-19. Mortality in this study is 33% for patients with ILD, compared with 13% for controls[5]. Lee et al. showed patients with ILD are not only more susceptible to COVID-19, but also more experience severe COVID-19 compared with those without ILD [6]. A recent study showed that COVID-19 patients with fibrotic ILD (including IPF) has a higher mortality rate than non-fibrotic ILD [7].

In contrast to vary ILD studies, very few data are available for primarly focused on patients with IPF. We therefore aimed to describe the characteristics and outcomes of IPF patients with confirmed COVID-19 infection.

2. MATERIAL AND METHODS

This retrospective, observational, multi-center study included consecutive patients with IPF diagnosed with a COVID-19 infection between March 14, 2020, and March 14, 2021. We collected all IPF patients diagnosed with COVID-19 at four tertiary ILD centers from four different cities, in Turkey. Diagnosis of IPF was based on the ATS/ERS/JRS/ALAT joint consensus report [8]. IPF diagnosis was based on clinical radiological parameters in 29/46 of patients (63%). Histological diagnosis of IPF/Usuall interstitial pneumonia (UIP) was obtained in 17 patients (37%). Patients must have a confirmatory COVID-19 polymerase chain reaction (PCR) to be included in the study. Clinically suspected cases and cases with close contact to COVID-19 confirmed cases were not included if either not tested or tested negative by PCR. COVID-19 positivity was defined as a positive result on real-time PCR (rt-PCR) assay of nasal and/or pharyngeal swab specimens.

Clinical data were collected from each institution's electronic medical record. The abstracted data included the following: age, sex, medical comorbidities, smoking history, body mass index (BMI), the presence of long term oxygen therapy (LTOT), pulmonary function test results including forced vital capacity (FVC (L)), FVC (%), diffusing capacity of the lungs for carbon monoxide *(*DLCO (%)), diffusing capacity divided by the alveolar volume (DLCO/VA), six minute walk test (6MWT), and minimum oxygen saturation (SO_2) on 6MWT. In addition clinical, and radiological features, treatment data, length of hospital and

intensive care unit (ICU) stays,intervention for respiratory failure and outcomes of COVID-19 were recorded. This study was approved by the Ethics Committee of the Akdeniz University School of Medicine (No: 502 Date: 07.07.2021). Written informed consent was not obtained from the patients since it is not required for retrospective studies in Turkey.

2.1.Statistical Analysis

The statistical analysis was carried out with IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp. To define the sample, continuous variables were expressed as mean ± standard deviation, median (minimum-maximum) and categorical variables as number and percentage. The normal distribution of the data was tested with Shapiro-Wilk normality test. Variables with a non-normal distribution were described as median and interquartile range (IQR), and analyzed by non-parametric tests. In order to assess the difference between categorical variables, Chi-square test was used. Independent Samples T Test was used to compare the data between two groups and Mann–Whitney U-test was used to compare the data without normal distribution. Logistic regression analysis was used to determine the predictors for mortality. Statistical significance level was accepted as 0.05.

3. RESULTS

We identified 77 patients with IPF who underwent testing for COVID-19, of whom 46 (59.7 %) were positive and included in our study. Of these, 33 (71.7%) were male and the mean age was 65±10 years. Forty-two patients (91.3%) had at least one comorbidity. Median IPF diagnosis was 3 years (range 1-8) and median antifibrotic treatment duration was 2 years (range 1-5). Of the whole cohort, 32 (69.6%) were on pirfenidone treatment and 14 (30.4%) were on nintedanib treatment when COVID-19 diagnosis was made. Antifibrotic treatment interrupted in 5 patients(10.9%) after COVID-19 diagnosis. Demographics features, smoking history, pulmonary function test results, pulmonary symptoms, radiological findings and treatments are summarized in Table 1.

Shortness of breath (58.7%), fever (45.7%) and cough (37%) were the most commonly reported COVID-19 symptoms. Forty-two patients (91.3%) underwent thorax computed tomography (CT). There were bilateral involvement in 37 patients (88.1%) and unilateral involvement in 5 patients (11.9%). Bilateral ground-glass opacities (GGO) were the main imaging features of the disease in thorax CT. Overall, 30 patients (65.2%) received anti-viral favipravir treatment, 32 patients (69.6%) received corticosteroid, 12 patients (26.1%) received plasma treatment and 14 patients (30.4%) received antibiotic treatment. In our series, 24/46 patients required admission which represents a hospitalization rate of 52.2%. Median length of hospital stay was 10 days (range 3–32). Of the 24 hospitalized patients, 16 were admitted to an ICU and median length of ICU stay was 8 days (range 4–10). Overall, the in hospital mortality for patients with IPF and COVID-19 was 28.2% (13/46), and the 30-day mortality was 21.7% (10/46).

Hospitalized patients were more likely to have fever (hospitalized: 54.2% vs non-hospitalized 36.4%, p=0.024), dyspnea (66.7% vs 50%, p=0.009), cough (54.2% vs 18.2%, p=0.001), consolidation on thorax CT (41.7% vs 4.6%, p<0.001) and more likely to use LTOT (26.1% vs 9.1%, p=0.003) (Table 2). There was no difference in other parameters. The mortality rate was higher in patients with lower DLCO/VA, who were on LTOT, who received plasma treatment and those who had consolidation in thorax CT (38.5% vs 18.2%, p=0.005) (Table 3). Mortality was not different in terms of radiographic extension (unilateral vs bilateral) (p=0.302). On multivariable analysis, neither factor was significantly associated with hospitalization or mortality for COVID-19 (Table 4, 5).

4. DISCUSSION

There are very few data about the course of COVID-19 infection in patients with IPF. In this study, we found that hospitalization, ICU requirement and mortality rates were high in IPF patients with COVID-19 infection. In our study, hospitalization rate, mortality rate, and ICU requirement rate were 52,2%, 28,2%, 66,7% respectively, while in the general population these rates were reported as 21-28% [9,10], 2,0% [1], 10-20% [9,10], respectively.

Some studies reported that COVID-19 is more common in patients with interstitial lung disease (ILD), while other studies showed that it is less common [6,11]. Recently, a large population-based study demonstrated that COVID-19 is 2.4 fold more frequent in patients with ILD compared to non-ILD patients [6]. As there was no control group in our study, we were unable to evaluate whether COVID-19 is more common in general population. However, 59.7% of our patients had positive rt-PCR result.

The course is more severe (such as the need for oxygen therapy, intensive care and, mechanical ventilation), and the risk of mortality is high if COVID-19 and ILD coexist [4–7,11,12]. Moreover, both increased susceptibility and a more severe disease course were found in the subgroup analysis of patients with IPF [6].Various studies showed that when patients with ILD had COVID-19 infection, 44-84% were hospitalized, 49.3-67.8% had severe disease and mortality rates were 13.4-15.9% [4–7,11,12]. Gallay et al. analyzed the survival of COVID-19 in patients with ILDs and compared mortality rates among those with fibrotic idiopathic ILDs, including IPF, with other ILDs [7]. In the study, hospitalization rate was 84% and ICU admission was 21% in fibrotic idiopathic ILD. The mortality rate in the fibrotic ILD group was 35% in this study [7]. Similarly, Drake et al. showed that COVID-19 infection was associated with higher mortality rate in patients with IPF when compared to the other ILD and without ILD patients [4].

It is unknown why COVID-19 is associated with poor prognosis in patients with IPF. It may be related to the decreased pulmonary reserve. Inflammation and lung damage in IPF may become more evident with the COVID-19 coexistence (especially during the cytokine storm) which may be associated with higher risk of death [13]. Advanced age, male gender, poor

lung function, and the presence of comorbidities are common risks for both IPF and severe COVID-19 infection [6–8]. Therefore, it may be speculated that a very serious clinical condition may develop if a patient with IPF is infected with COVID-19 [3]. It has been shown that the expression of ACE2 and TMPRSS2, which are the keys of SARS-CoV-2 entrance to body, is increased in patients with IPF and may be associated with a more severe disease presentation [14]. It has also been shown that ACE2 expression is increased in lung fibroblasts of patients with IPF [15].

There are few studies investigating the effects of COVID-19 infection in patients with IPF. In a study, Naqvi et al. investigated the effect of COVID-19 in 251 patients with IPF. The hospitalization rate was 44% and the mortality rate was 15.9% [12]. In our study, the hospitalization rate was slightly higher (47.8%) and the mortality rate was pretty higher (28.2%).

In a single center small study from China, Huang et al. showed that COVID-19 patients with ILD were more likely to have cough, sputum, fatigue, dyspnea and diarrhea [11]. Similarly, dyspnea, cough, and fever were the most leading symptoms of our patients. We also found that hospitalization rate was high in patients who had have fever, dyspnea, cough, who were on LTOT and GGO in thorax CT.

Multiple prognostic factors have been described in COVID-19 patients with pre-existing ILD ([4–6,11,16]. These are advanced age, young age, lower DLCO, UIP pattern, FVC<80%, obesity, male sex, neutrophils counts, pro-inflammatory cytokines, and coagulation dysfunction biomarkers. In our study, none of the factor was associated with poor outcome such as hospitalization or mortality. In the current study, consolidation finding on chest CT was more frequently found in hospitalized patients vs outpatients (41.7 % vs 4.6 %, p<0.001) and patients who died vs who survived (38.5% vs 18.2%, p=0.02). The presence of consolidation on chest CT is a late finding and may be associated with mortality as shown in several studies [17–19].

Our study had several limitations: 1) It is possible that there are additional confounding variables for which we did not account, 2) Absence of control group may undervalue our study, 3) Given the limited sensitivity of real-time PCR for COVID-19, it is possible that we missed additional cases who were negative by this initial testing modality, 4) Our cohort consisted of patients with mild to moderate IPF who received antifibrotic therapy and were followed up more carefully. Patients with severe IPF were not represented in our study, 5) There might be some missing patients who did not undergo PCR testing because of mild COVID-19 disease. Our study represents the more severe cases of COVID and it is possible that milder cases were missed, but this does not impact the overall conclusion that COVID-19 course may be severe in patients with IPF. On the other hand, the major strength of this study is that we included the largest number of IPF patients with COVID-19.

5. CONCLUSIONS

In conclusion, patients with IPF may represent a vulnerable population for COVID-19 because of high rates of hospitalization, ICU requirement, and mortality. It is clear that during the pandemic period, IPF patients should show extreme attention for self-protection, have the

priority for vaccination, and be followed very carefully in the presence of COVID-19. In addition, it should be ensured that they receive the optimum treatment of IPF as much as possible.

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Table 1. Baseline demographics and disease characteristics*

Characteristics	n=46
Age, years	65±10
Male sex, n(%)	33 (71.7)
Ever smoker, n(%)	24 (52.2)
BMI, kg/m^2	28.8±4.3
Comorbidity, n(%)	42 (91.3)
Hypertension	19 (41.3)
Coronary artery disease	15 (32.6)
Diabetes mellitus	9 (19.6)
FVC, L	2.34±0.83
FVC, %	71.8±23.5
DLCO, %	44±17
DLCO/VA, %	64±22
6 MWT, m	336±90
SPO_2, min	89±5
COVID-19 symptoms, n(%)	
Dyspnea	27 (58.7)
Fever	21 (45.7)
Cough	17 (37.0)
Treatment setting, n(%)	
Inpatient	24 (52.2)
Outpatient	22 (47.8)
Patients who underwent CT n(%)	42 (91.3)
CT pattern	
Ground glass opacities	35 (83.3)

Consolidation	11 (26.1)
Other	19 (45.2)
Respiratory support (n=16), n(%)	
Mechanical ventilation	10 (62.5)
Non-invasive mechanical ventilation	9 (56.2)
High-flow	6 (37.5)
Length of hospital stay (day) (median) (min-max)	10 (3-32)
Length of ICU stay (day) (median) (min-max)	8 (4-10)

BMI: Body mass index; MWT: minute walk test; ICU: intensive care unit; CT: computed tomography
*Data are mean (SD) based on N unless stated otherwise. Percentages are based on N unless stated otherwise

Table 2. Comparison of patients who were treated inpatient or outpatient*

	Outpatient (n=22), n (%)	Inpatient (n=24) n (%)	P
Male sex	13 (59.1)	14 (58.3)	
Age, years	65±9	65±11	0.97
BMI, kg/m^2	28.9±4.5	28.7±4.2	0.87
FVC (L) (IQR)	2.2 (0.8)	2.4 (0.79)	0.61
FVC, %	77.1±19.5	67.0±26.2	0.20
DLCO, %	50±14	39±19	0.07
DLCO/VA, %	68±22	60±22	0.29
6 MWT (m) (IQR)	320 (135)	380 (150)	0.96
SPO2 (min) (IQR)	91 (7)	89 (4)	0.21
Fever	8 (36.4)	13 (54.2)	**0.02**
Dyspnea	11 (50)	16 (66.7)	**<0.001**
Cough	4 (18.2)	13 (54.2)	**<0.001**
Consolidaton	1 (4.6)	10 (41.7)	**<0.001**
Systemic steroid use	14 (63.6)	18 (75)	0.09
Favipiravir	11 (50)	12 (50)	0.60
Antibiotic use	6 (27.3)	8 (33.3)	0.431
Comorbidity	18 (81.8)	18 (75)	0.48
LTOT	2 (9.1)	12 (26.1)	**<0.001**

BMI: Body mass index; MWT: minute walk test; LTOT: long term oxygen therapy

*Data are mean (SD) based on N unless stated otherwise. Percentages are based on N unless stated otherwise

Table 3. Comparison of patients who died or survived*

	Died (n=13) n (%)	Survived (n=33) n (%)	p
Age, years	61±10.6	65.9±9.8	0.77
BMI, kg/m^2	30.8±4.8	28.2±4.0	0.23
FVC (L)	2.0±0.8	2.4±0.7	0.30
FVC, %	63.2±13.3	75.5±78.7	0.22
DLCO, %	35.6±12.6	47.8±14.1	0.14
Pirfenidon	11 (84.6)	20 (60.6)	0.17
DLCO/VA	51.21±19.0	68.4±21.2	**0.03**
6 MWT (m)	277.5±13.7	352.0±73.8	0.33
SPO_2 (min)	87.2±4.7	89.3±4.8	0.26
Fever	4 (30.8)	17 (51.5)	1.00
Dyspnea	7 (53.9)	20 (60.6)	0.07
Cough	4 (30.8)	13 (39.4)	0.43
Consolidation	5 (38.5)	6 (18.2)	**0.005**
Systemic corticosteroid use	7 (53.9)	25 (75.8)	1.00
Plasma treatment	6 (38.5)	6 (18.2)	**0.00**
Favipiravir	5 (38.5)	18 (54.6)	1.00
Antibiotic use	5 (38.5)	9 (27.3)	0.10
Comorbidity	11 (84.6)	31 (93.9)	0.56
Male sex	9 (69.2)	19 (57.6)	0.69
LTOT	7 (53.9)	7 (21.2)	**0.04**

BMI: Body mass index; MWT: minute walk test; LTOT: long term oxygen treatment

*Data are mean (SD) based on N unless stated otherwise. Percentages are based on N unless stated otherwise

Table 4. Multivariable analyses for risk of hospitalization

	B	S.E.	Sig.	Exp (B)
Pirfenidone use	0.06	0.87	0.93	1.07
Comorbidity	20.93	28410.67	0.99	1.08
LTOT	0.87	1.13	0.43	2.40
BMI, kg/m^2	-0.05	0.09	0.59	0.94
FVC, %	-0.00	0.02	0.87	0.99
DLCO, %	-0.00	0.03	0.88	0.99

BMI: Body mass index; LTOT: long term oxygen treatment

Table 5. Multivariable analyses for COVID-19 related death

	B	S.E.	Sig.	Exp (B)
Pirfenidone use	-20.50	11783.60	0.99	0.00
Comorbidity	19.41	40192.96	1.00	2.69
LTOT	-0.92	1.823	0.61	0.39
BMI, kg/m^2	0.28	0.25	0.27	1.32
FVC, %	0.04	0.04	0.31	1.04
DLCO, %	-0.11	0.07	0.14	0.89
Corticosteroid treatment	18.61	24029.17	0.99	1.21

LTOT: long term oxygen treatment; BMI: Body mass index